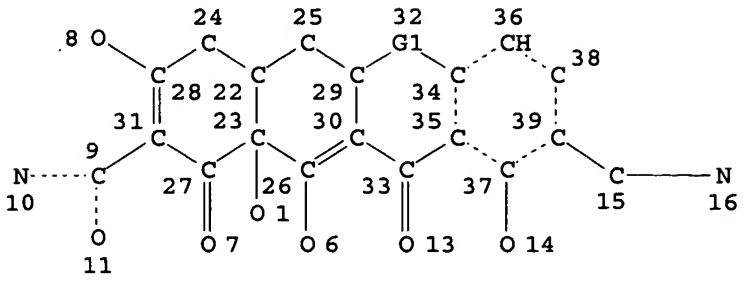
L5 HAS NO ANSWERS
L5 STR



VAR G1=O/S/C/N
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 29

STEREO ATTRIBUTES: NONE

=> s l5 ful
FULL SEARCH INITIATED 08:00:33 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 7865 TO ITERATE

100.0% PROCESSED 7865 ITERATIONS 50 ANSWERS
SEARCH TIME: 00.00.01

L11 50 SEA SSS FUL L5

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	166.94	199.10

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-2.25

FILE 'CAPLUS' ENTERED AT 08:00:37 ON 16 FEB 2006

FILE COVERS 1907 - 16 Feb 2006 VOL 144 ISS 8
FILE LAST UPDATED: 15 Feb 2006 (20060215/ED)

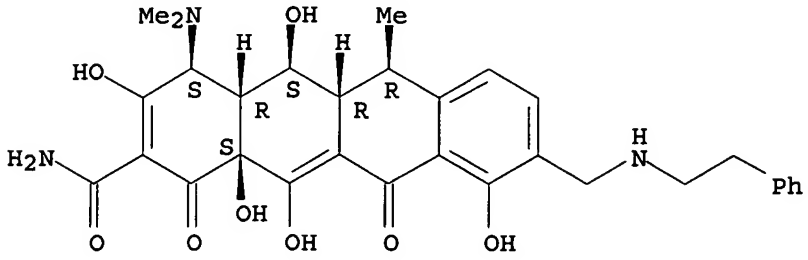
Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

```
=> s l11
L12         11 L11

=> s l12 and py<=2002
      22790887 PY<=2002
L13          2 L12 AND PY<=2002

=> d bib abs hitstr 1-2

L13  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2002:716035  CAPLUS
DN   137:244598
TI   Substituted tetracycline compounds as synergistic antifungal agents
IN   Draper, Michael; Nelson, Mark L.
PA   Paratek Pharmaceuticals, Inc., USA
SO   PCT Int. Appl., 114 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
PI   WO 2002072031         A2    20020919    WO 2002-US7829          20020314 <--
     WO 2002072031         A3    20031113
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, UZ, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB,
             GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA,
             GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2440757            AA    20020919    CA 2002-2440757         20020314 <--
     US 2003166585         A1    20030904    US 2002-97634           20020314
     EP 1381372            A2    20040121    EP 2002-750617          20020314
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
     JP 2005504722         T2    20050217    JP 2002-570991          20020314
     US 2005070510         A1    20050331    US 2004-943571          20040916
PRAI US 2001-275899P       P     20010314
     US 2002-97634         A1    20020314
     WO 2002-US7829        W     20020314
OS   MARPAT 137:244598
AB   Methods and compns. for treating for the synergistic treatment of fungal
     associated disorders are discussed.  The method includes administering the
     antifungal agent with an effective amount of a substituted tetracycline
     compound, such that the antifungal activity of the antifungal agent is
     increased.  Examples of antifungal agents include polyenes such as
     amphotericin B.
IT   460073-43-2P
     RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological
     activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL
     (Biological study); PREP (Preparation); USES (Uses)
        (substituted tetracycline compds. as synergistic antifungal agents in
        relation to cytotoxicity)
RN   460073-43-2  CAPLUS
CN   2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-
```

3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-9-[[(2-phenylethyl)amino]methyl]-, (4S,4aR,5S,5aR,6R,12aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

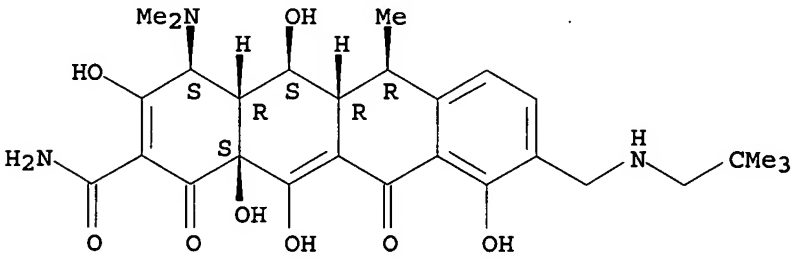


IT 460073-40-9 460073-41-0 460073-53-4
460076-23-7
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(substituted tetracycline compds. as synergistic antifungal agents in relation to cytotoxicity)

RN 460073-40-9 CAPLUS

CN 2-Naphthacenecarboxamide, 4-(dimethylamino)-9-[[(2,2-dimethylpropyl)amino]methyl]-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, (4S,4aR,5S,5aR,6R,12aS)- (9CI) (CA INDEX NAME)

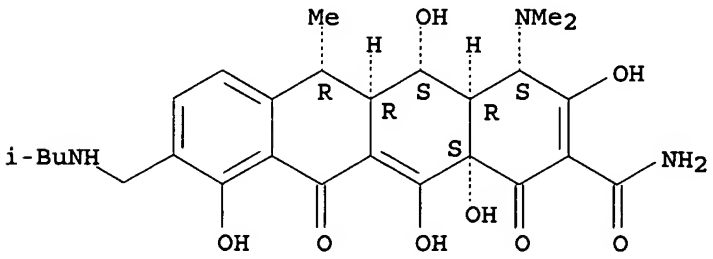
Absolute stereochemistry.



RN 460073-41-0 CAPLUS

CN 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-9-[[(2-methylpropyl)amino]methyl]-1,11-dioxo-, (4S,4aR,5S,5aR,6R,12aS)- (9CI) (CA INDEX NAME)

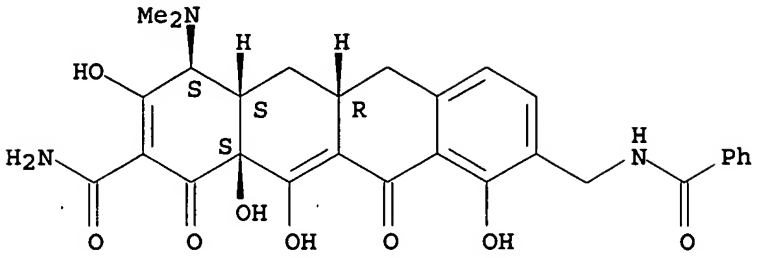
Absolute stereochemistry.



RN 460073-53-4 CAPLUS

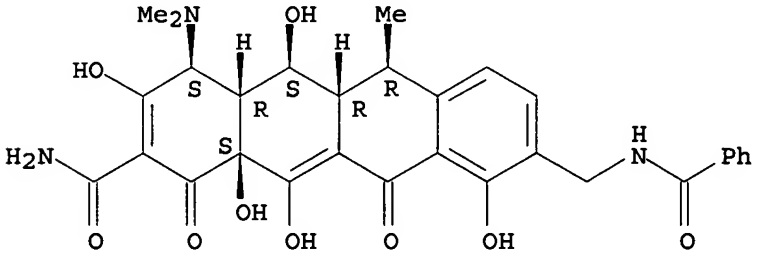
CN 2-Naphthacenecarboxamide, 9-[(benzoylamino)methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, (4S,4aS,5aR,12aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 460076-23-7 CAPLUS
CN 2-Naphthacenecarboxamide, 9-[(benzoylamino)methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, (4S,4aR,5S,5aR,6R,12aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
AN 1963:448189 CAPLUS
DN 59:48189
OREF 59:8679a-b
TI Tetracycline derivatives
PA Carlo Erba Societa per Azioni
SO 3 pp.
DT Patent
LA Unavailable

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI GB 921252		19630320	GB	<--
DE 1147576			DE	
PRAI IT		19600309		

AB H2O-soluble tetracycline derivs. are prepared with HCHO and an α-amino acid amide. For example, 0.6 cc. 38% HCHO and 0.6 g. l-alaninamide are added to a solution containing 3 g. tetracycline in 120 ml. MeOH. After 2 hrs., the clear solution is evaporated and diluted with Et2O to precipitate the solid, which is filtered off and dried in vacuo at 50°, m. 150-6°, C26H32N4O9.

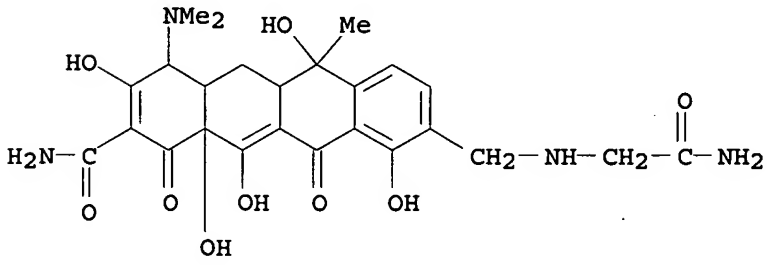
IT **96670-08-5**, 2-Naphthacenecarboxamide, 9-[[(carbamoylmethyl)amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-
96867-69-5, 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-9-[[[1-[(2-hydroxyethyl)carbamoyl]ethyl]amino]methyl]-6-methyl-1,11-dioxo-
96967-72-5, 2-Naphthacenecarboxamide, 9-[[(1-carbamoylethyl)amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-

96967-73-6, 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-9-[[[(methylcarbamoyl)methyl]amino]methyl]-1,11-dioxo- **97828-43-8**, 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-9-[[[[(2-hydroxyethyl)carbamoyl]methyl]amino]methyl]-6-methyl-1,11-dioxo- **97879-49-7**, 2-Naphthacenecarboxamide, 9-[[[5-amino-1-[(2-hydroxyethyl)carbamoyl]pentyl]amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- **97924-11-3**, 2-Naphthacenecarboxamide, 9-[[(5-amino-1-carbamoylpentyl)amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-

(preparation of)

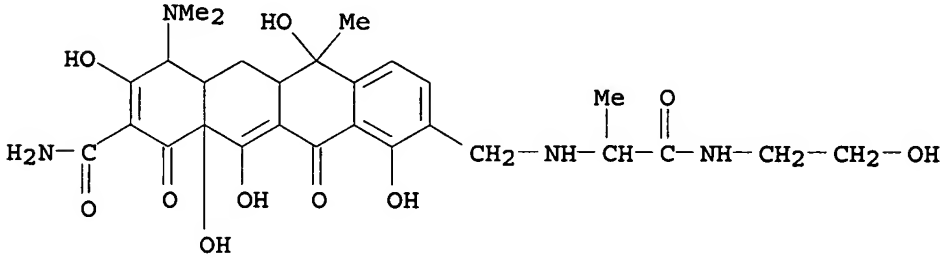
RN 96670-08-5 CAPLUS

CN 2-Naphthacenecarboxamide, 9-[[(carbamoylmethyl)amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- (7CI) (CA INDEX NAME)



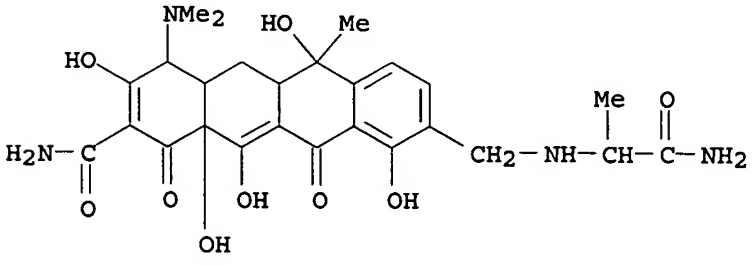
RN 96867-69-5 CAPLUS

CN 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-9-[[[1-[(2-hydroxyethyl)carbamoyl]ethyl]amino]methyl]-6-methyl-1,11-dioxo- (7CI) (CA INDEX NAME)

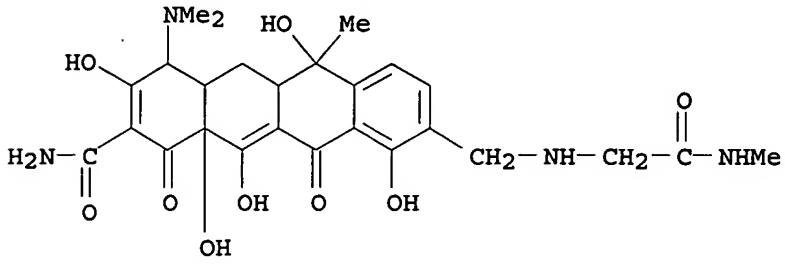


RN 96967-72-5 CAPLUS

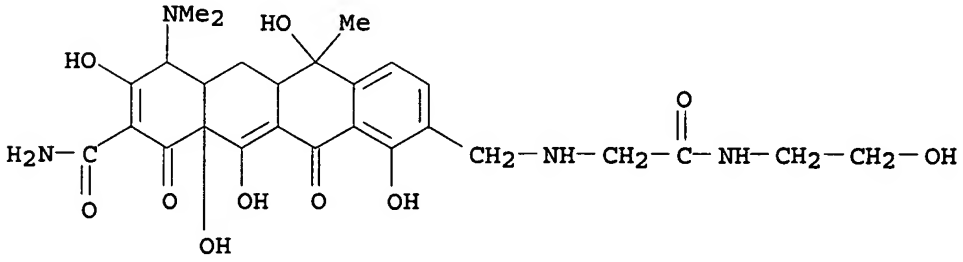
CN 2-Naphthacenecarboxamide, 9-[[(1-carbamoylethyl)amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- (7CI) (CA INDEX NAME)



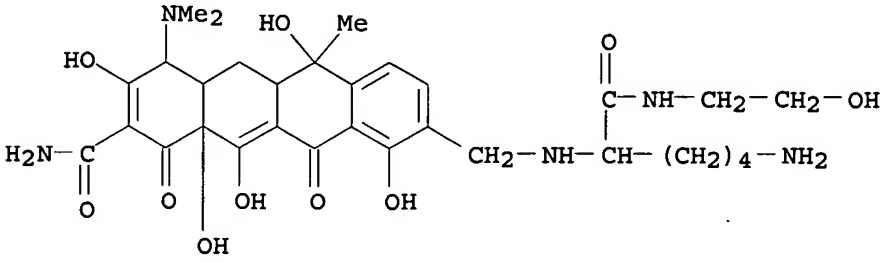
RN 96967-73-6 CAPLUS
CN 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-9-[[[(methylcarbamoyl)methyl]amino]methyl]-1,11-dioxo- (7CI) (CA INDEX NAME)



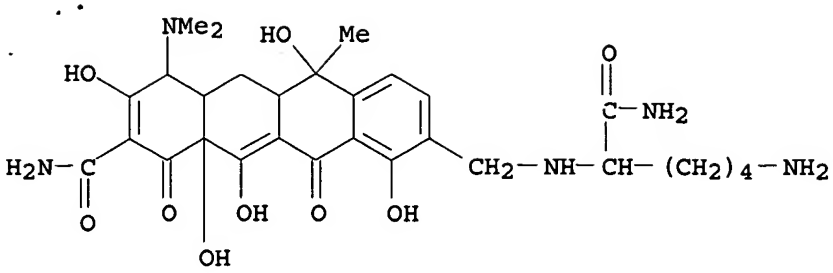
RN 97828-43-8 CAPLUS
CN 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-9-[[[[(2-hydroxyethyl)carbamoyl]methyl]amino]methyl]-6-methyl-1,11-dioxo- (7CI) (CA INDEX NAME)



RN 97879-49-7 CAPLUS
CN 2-Naphthacenecarboxamide, 9-[[[5-amino-1-[(2-hydroxyethyl)carbamoyl]pentyl]amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- (7CI) (CA INDEX NAME)



RN 97924-11-3 CAPLUS
CN 2-Naphthacenecarboxamide, 9-[[(5-amino-1-carbamoylpentyl)amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- (7CI) (CA INDEX NAME)


NMe2
HO
Me
HO
O
C—NH2
H2N—C
O
O
OH
O
OH
OH
CH2—NH—CH—(CH2)4—NH2

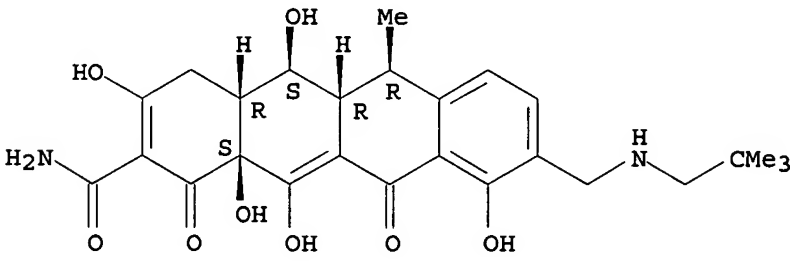
AN 2004:633439 CAPLUS
DN 141:167771
TI Tetracycline compounds having target therapeutic activities
IN Levy, Stuart B.; Draper, Michael; Nelson, Mark L.; Jones, Graham
PA Paratek Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 277 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004064728	A2	20040805	WO 2004-US1036	20040116
	WO 2004064728	A3	20041216		

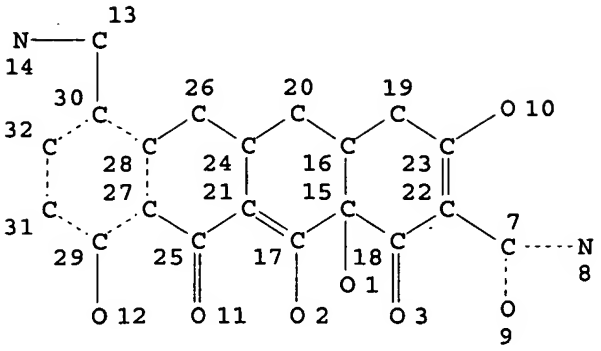
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

PRAI US 2003-441141P P 20030116
OS MARPAT 141:167771
AB Methods and compds. for treating diseases, e.g. inflammation process-associated states, with tetracycline compds. having a target therapeutic activity are described. Preparation of selected tetracycline compds. is described.
IT **731026-89-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetracycline compds. with target therapeutic activities)
RN 731026-89-4 CAPLUS
CN 2-Naphthacenecarboxamide, 9-[[(2,2-dimethylpropyl)amino]methyl]-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, (4aR,5S,5aR,6R,12aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



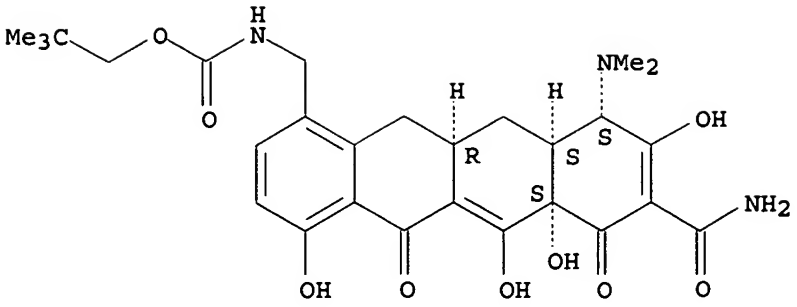
=> d l1
L1 HAS NO ANSWERS
L1 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 29

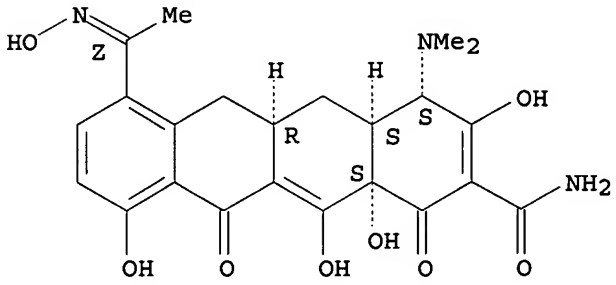
STEREO ATTRIBUTES: NONE



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L12 5 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN
IN 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-7-[(1Z)-1-(hydroxyimino)ethyl]-1,11-dioxo-, (4S,4aS,5aR,12aS)- (9CI)
MF C23 H25 N3 O8

Absolute stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

=> s (C26 H31 N3 O9/mf or C28 H35 N3 O9/mf) and l12
58 C26 H31 N3 O9/MF
47 C28 H35 N3 O9/MF
L13 2 (C26 H31 N3 O9/MF OR C28 H35 N3 O9/MF) AND L12

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	179.68	251.13

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-0.75

FILE 'CAPLUS' ENTERED AT 16:21:44 ON 15 FEB 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 15 Feb 2006 VOL 144 ISS 8
FILE LAST UPDATED: 14 Feb 2006 (20060214/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> s l13
L14 6 L13

=> d bib 1-6

L14 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:1036703 CAPLUS
DN 141:420412
TI Substituted tetracycline compounds for the treatment of malaria
IN Draper, Michael; Nelson, Mark L.
PA USA
SO U.S. Pat. Appl. Publ., 590 pp., Cont.-in-part of U.S. Ser. No. 128,990, abandoned.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004242548	A1	20041202	US 2003-692563	20031024
	US 2004092490	A1	20040513	US 2002-128990	20020424
PRAI	US 2001-286193P	P	20010424		
	US 2002-128990	B2	20020424		
	US 2002-421259P	P	20021024		

OS MARPAT 141:420412

L14 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:371069 CAPLUS
DN 140:386006
TI Substituted tetracycline compounds for the treatment of malaria
IN Draper, Michael; Nelson, Mark L.
PA Paratek Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 161 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004038001	A2	20040506	WO 2003-US33927	20031024

```
     WO 2004038001          A3     20041111
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
             GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
             LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
             OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
             TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2502464             AA     20040506    CA 2003-2502464         20031024
     EP 1556007             A2     20050727    EP 2003-781398          20031024
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     JP 2006503898          T2     20060202    JP 2004-547165          20031024
PRAI US 2002-421259P        P      20021024
     WO 2003-US33927        W      20031024
OS   MARPAT 140:386006

L14  ANSWER 3 OF 6  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2004:371068  CAPLUS
DN   140:386057
TI   Methods of using substituted tetracycline compounds to modulate RNA, and
     therapeutic use
IN   Levy, Stuart B.; Draper, Michael; Jones, Graham; Nelson, Mark L.
PA   Paratek Pharmaceuticals, Inc., USA
SO   PCT Int. Appl., 124 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.             KIND   DATE        APPLICATION NO.         DATE
     ---------------        ----   --------    --------------------    --------
PI   WO 2004038000          A2     20040506    WO 2003-US33926         20031024
     WO 2004038000          A3     20041111
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
             GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
             LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ,
             OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
             TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2503446             AA     20040506    CA 2003-2503446         20031024
     US 2004214800          A1     20041028    US 2003-692764          20031024
     EP 1562608             A2     20050817    EP 2003-781397          20031024
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     JP 2006503897          T2     20060202    JP 2004-547164          20031024
PRAI US 2002-421248P        P      20021024
     WO 2003-US33926        W      20031024
OS   MARPAT 140:386057

L14  ANSWER 4 OF 6  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2003:57866  CAPLUS
DN   138:117673
TI   Tetracycline compounds having target therapeutic activities
IN   Levy, Stuart B.; Draper, Michael; Nelson, Mark L.; Jones, Graham
PA   Paratek Pharmaceuticals, Inc., USA
SO   PCT Int. Appl., 158 pp.
     CODEN: PIXXD2
```

DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003005971	A2	20030123	WO 2002-US22451	20020715
	WO 2003005971	A3	20031127		
	WO 2003005971	C1	20040506		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004063674	A1	20040401	US 2002-196010	20020715
	EP 1408987	A2	20040421	EP 2002-748169	20020715
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	JP 2004537544	T2	20041216	JP 2003-511780	20020715
PRAI	US 2001-305546P	P	20010713		
	US 2002-395741P	P	20020712		
	WO 2002-US22451	W	20020715		

OS MARPAT 138:117673

L14 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:716035 CAPLUS
DN 137:244598
TI Substituted tetracycline compounds as synergistic antifungal agents
IN Draper, Michael; Nelson, Mark L.
PA Paratek Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002072031	A2	20020919	WO 2002-US7829	20020314
	WO 2002072031	A3	20031113		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2440757	AA	20020919	CA 2002-2440757	20020314
	US 2003166585	A1	20030904	US 2002-97634	20020314
	EP 1381372	A2	20040121	EP 2002-750617	20020314
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2005504722	T2	20050217	JP 2002-570991	20020314
	US 2005070510	A1	20050331	US 2004-943571	20040916
PRAI	US 2001-275899P	P	20010314		
	US 2002-97634	A1	20020314		
	WO 2002-US7829	W	20020314		

OS MARPAT 137:244598

L14 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:51420 CAPLUS
DN 136:102232
TI Preparation of 7-substituted tetracycline derivatives for pharmaceutical use as antibacterial agents
IN Nelson, Mark L.; Frechette, Roger; Viski, Peter; Ismail, Mohamed; Bowser, Todd; Bhatia, Beena; Messersmith, David; McIntyre, Laura; Koza, Darrell; Rennie, Glen; Sheahan, Paul; Hawkins, Paul; Verma, Atul; Warchol, Tad; Bandarage, Upul
PA Trustees of Tufts College, USA; Paratek Pharmaceuticals, Inc.
SO PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002004407	A2	20020117	WO 2001-US20766	20010629
	WO 2002004407	A3	20020404		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2415718	AA	20020117	CA 2001-2415718	20010629
	US 2003055025	A1	20030320	US 2001-895812	20010629
	US 6818635	B2	20041116		
	EP 1301466	A2	20030416	EP 2001-950674	20010629
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2001012265	A	20030624	BR 2001-12265	20010629
	JP 2004502753	T2	20040129	JP 2002-509075	20010629
	ZA 2003000750	A	20040211	ZA 2003-750	20030127
	US 2004224928	A1	20041111	US 2004-853635	20040524
PRAI	US 2000-216760P	P	20000707		
	US 2001-275576P	P	20010313		
	US 2001-895812	A1	20010629		
	WO 2001-US20766	W	20010629		

OS MARPAT 136:102232

L6 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:99455 CAPLUS
DN 142:197754
TI Preparation of substituted tetracycline analogs for use in antibiotic pharmaceutical compositions
IN Nelson, Mark L.; Ohemeng, Kwasi; Amoo, Victor; Kim, Oak; Abato, Paul; Assefa, Haregewein; Berniac, Joel; Bhatia, Beena; Bowser, Todd; Chen, Jackson; Grier, Mark; Hohos, Aaron; Honeyman, Laura; Ismail, Mohamed Y.; Mechiche, Rachid; Nihlawi, Mohammed; Sizensky, Emmanuelle
PA Paratek Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005009943	A2	20050203	WO 2004-US20249	20040625
	WO 2005009943	A3	20050616		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2005143352	A1	20050630	US 2004-877928	20040625
PRAI	US 2003-486017P	P	20030709		
	US 2003-525287P	P	20031125		
	US 2003-530123P	P	20031216		

OS MARPAT 142:197754

L6 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:1036703 CAPLUS
DN 141:420412
TI Substituted tetracycline compounds for the treatment of malaria
IN Draper, Michael; Nelson, Mark L.
PA USA
SO U.S. Pat. Appl. Publ., 590 pp., Cont.-in-part of U.S. Ser. No. 128,990, abandoned.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004242548	A1	20041202	US 2003-692563	20031024
	US 2004092490	A1	20040513	US 2002-128990	20020424
PRAI	US 2001-286193P	P	20010424		
	US 2002-128990	B2	20020424		
	US 2002-421259P	P	20021024		

OS MARPAT 141:420412

L6 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:633439 CAPLUS
DN 141:167771
TI Tetracycline compounds having target therapeutic activities
IN Levy, Stuart B.; Draper, Michael; Nelson, Mark L.; Jones, Graham
PA Paratek Pharmaceuticals, Inc., USA

SO PCT Int. Appl., 277 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004064728	A2	20040805	WO 2004-US1036	20040116
WO 2004064728	A3	20041216		

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

PRAI US 2003-441141P P 20030116
OS MARPAT 141:167771

L6 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:371069 CAPLUS
DN 140:386006
TI Substituted tetracycline compounds for the treatment of malaria
IN Draper, Michael; Nelson, Mark L.
PA Paratek Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 161 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004038001	A2	20040506	WO 2003-US33927	20031024
WO 2004038001	A3	20041111		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2502464	AA	20040506	CA 2003-2502464	20031024
EP 1556007	A2	20050727	EP 2003-781398	20031024

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

JP 2006503898	T2	20060202	JP 2004-547165	20031024

PRAI US 2002-421259P P 20021024
WO 2003-US33927 W 20031024
OS MARPAT 140:386006

L6 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:371068 CAPLUS
DN 140:386057
TI Methods of using substituted tetracycline compounds to modulate RNA, and therapeutic use
IN Levy, Stuart B.; Draper, Michael; Jones, Graham; Nelson, Mark L.
PA Paratek Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004038000	A2	20040506	WO 2003-US33926	20031024
	WO 2004038000	A3	20041111		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2503446	AA	20040506	CA 2003-2503446	20031024
	US 2004214800	A1	20041028	US 2003-692764	20031024
	EP 1562608	A2	20050817	EP 2003-781397	20031024
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP 2006503897	T2	20060202	JP 2004-547164	20031024
PRAI	US 2002-421248P	P	20021024		
	WO 2003-US33926	W	20031024		

OS MARPAT 140:386057

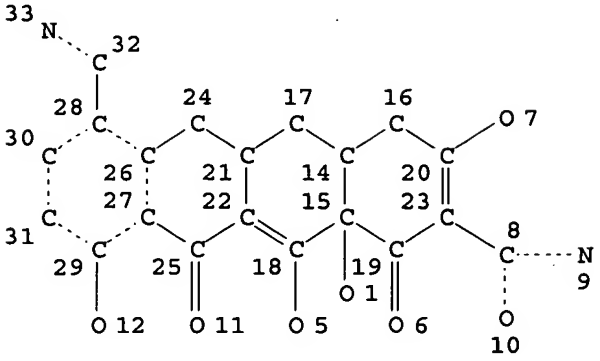
L6 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:57866 CAPLUS
DN 138:117673
TI Tetracycline compounds having target therapeutic activities
IN Levy, Stuart B.; Draper, Michael; Nelson, Mark L.; Jones, Graham
PA Paratek Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DT Patent
LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003005971	A2	20030123	WO 2002-US22451	20020715
	WO 2003005971	A3	20031127		
	WO 2003005971	C1	20040506		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004063674	A1	20040401	US 2002-196010	20020715
	EP 1408987	A2	20040421	EP 2002-748169	20020715
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	JP 2004537544	T2	20041216	JP 2003-511780	20020715
PRAI	US 2001-305546P	P	20010713		
	US 2002-395741P	P	20020712		
	WO 2002-US22451	W	20020715		

OS MARPAT 138:117673

```
=> d l5
L5 HAS NO ANSWERS
L5                STR
```

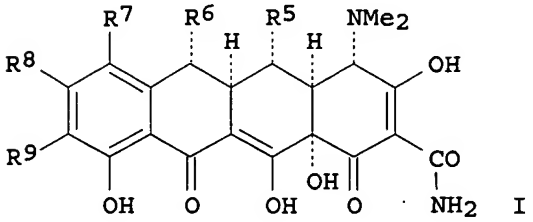



```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  29

STEREO ATTRIBUTES: NONE


=> s l5
SAMPLE SEARCH INITIATED 16:02:20 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -       22 TO ITERATE

100.0% PROCESSED       22 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          159 TO      721
PROJECTED ANSWERS:               0 TO        0

L6             0 SEA SSS SAM L5

=> s l5 ful
FULL SEARCH INITIATED 16:02:24 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      483 TO ITERATE

100.0% PROCESSED      483 ITERATIONS                                3 ANSWERS
SEARCH TIME: 00.00.01

L7             3 SEA SSS FUL L5
```

L8 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:99455 CAPLUS
DN 142:197754
TI Preparation of substituted tetracycline analogs for use in antibiotic pharmaceutical compositions
IN Nelson, Mark L.; Ohemeng, Kwasi; Amoo, Victor; Kim, Oak; Abato, Paul; Assefa, Haregewein; Berniac, Joel; Bhatia, Beena; Bowser, Todd; Chen, Jackson; Grier, Mark; Hohos, Aaron; Honeyman, Laura; Ismail, Mohamed Y.; Mechiche, Rachid; Nihlawi, Mohammed; Sizensky, Emmanuelle
PA Paratek Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005009943	A2	20050203	WO 2004-US20249	20040625
	WO 2005009943	A3	20050616		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2005143352	A1	20050630	US 2004-877928	20040625
PRAI	US 2003-486017P	P	20030709		
	US 2003-525287P	P	20031125		
	US 2003-530123P	P	20031216		

OS MARPAT 142:197754
GI



I

AB Novel tetracycline analogs, such as I [R5 = R6 = H; R5 = OH, R6 = Me; R7 = H, Et, CH2NH2, NR9aR9b, perhaloalkenyl, substituted-Ph, -pyridinyl, -pyrazinyl, -furanyl, pyrazolyl; R8 = H, OH, SH, halogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfonyl, alkylsulfinyl, etc.; R9 = H, CH2NR9aR9b; R9a, R9b = H, alkyl, alkenyl; NR9aR9b = nitrogen linked heterocyclyl], were prepared for therapeutic uses, such as treating bacterial infections, viral infections, parasitic infections, especially malaria, and neoplasms, as well as other known applications for tetracycline compds. such as blocking tetracycline efflux and modulation of gene expression. Thus, I [R5 = R6 = R8 = H, R7 = 6-fluoropyridin-2-yl, R9 = CH2N(Me)CH2CH:CH2] was prepared via aromatic coupling of 7-iodosancycline I [R5 = R6 = R8 = R9 = H, R7 = iodo] with 6-fluoropyridin-3-ylboronic acid using Pd(dppf)2Cl2 and Na2CO3 in DMF and H2O, formylation of the coupled product I [R5 = R6 = R8 = R9 = H, R7 = 6-fluoropyridin-2-yl], and finally,

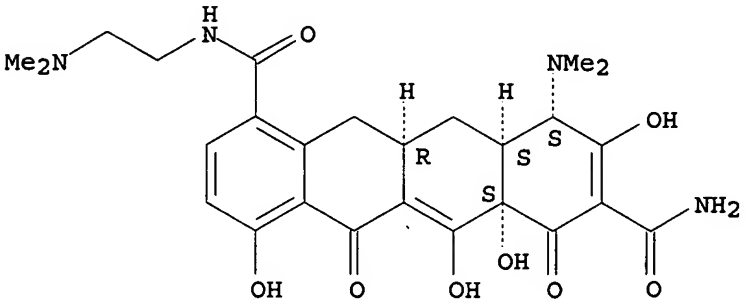
amination of the resulting formyl deriv, I [R5 = R6 = R8 = H, R7 = 6-fluoropyridin-2-yl, R9 = CHO] with MeNHCH2CH:CH2. The prepared tetracycline analogs were assayed in vitro for min. inhibitory concentration of common bacteria, such as E. coli, S.aureus, and Enterococcus sp.

IT **835884-34-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of substituted tetracycline analogs for therapeutic uses as antibiotics)

RN 835884-34-9 CAPLUS

CN 1,8-Naphthacenedicarboxamide, 10-(dimethylamino)-N1-[2-(dimethylamino)ethyl]-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-5,7-dioxo-, (6aS,10S,10aS,11aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L8 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN

AN 2004:1036703 CAPLUS

DN 141:420412

TI Substituted tetracycline compounds for the treatment of malaria

IN Draper, Michael; Nelson, Mark L.

PA USA

SO U.S. Pat. Appl. Publ., 590 pp., Cont.-in-part of U.S. Ser. No. 128,990, abandoned.
CODEN: USXXCO

DT Patent

LA English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2004242548	A1	20041202	US 2003-692563	20031024
	US 2004092490	A1	20040513	US 2002-128990	20020424
PRAI	US 2001-286193P	P	20010424		
	US 2002-128990	B2	20020424		
	US 2002-421259P	P	20021024		

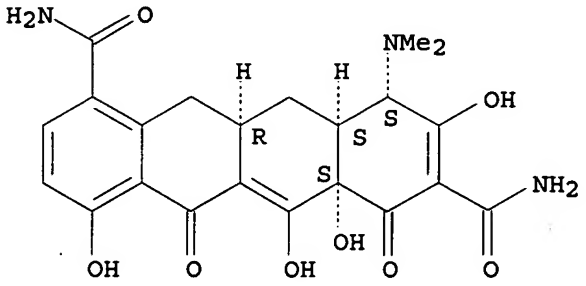
OS MARPAT 141:420412

AB The invention provides a method for treating or preventing malaria in a subject. The method includes administering an effective amount of a substituted tetracycline compound, such that malaria is treated or prevented. In one aspect, the invention relates to pharmaceutical compns. which include an effective amount of a tetracycline compound to treat malaria in a subject and a pharmaceutically acceptable carrier. The substituted tetracycline compds. of the invention can be used to in combination with one or more antimalarial compds. or can be used to treat or prevent malaria which is resistant to one or more other antimalarial compds. Preparation of e.g. sancycline derivs. is described.

IT **685859-18-1**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(substituted tetracycline compds. for treatment of malaria)
RN 685859-18-1 CAPLUS
CN 1,8-Naphthacenedicarboxamide, 10-(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-5,7-dioxo-, (6aS,10S,10aS,11aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



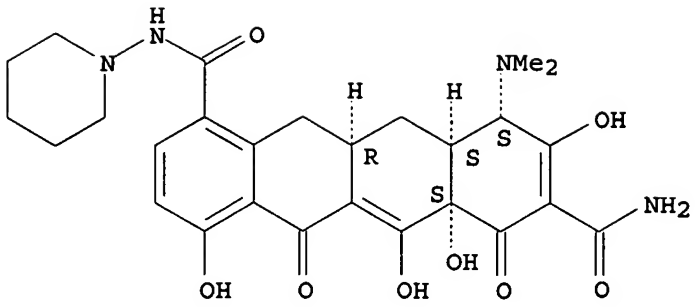
L8 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:633439 CAPLUS
DN 141:167771
TI Tetracycline compounds having target therapeutic activities
IN Levy, Stuart B.; Draper, Michael; Nelson, Mark L.; Jones, Graham
PA Paratek Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 277 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004064728	A2	20040805	WO 2004-US1036	20040116
WO 2004064728	A3	20041216		

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

PRAI US 2003-441141P P 20030116
OS MARPAT 141:167771
AB Methods and compds. for treating diseases, e.g. inflammation process-associated states, with tetracycline compds. having a target therapeutic activity are described. Preparation of selected tetracycline compds. is described.
IT **488818-96-8**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetracycline compds. with target therapeutic activities)
RN 488818-96-8 CAPLUS
CN 1,8-Naphthacenedicarboxamide, 10-(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-5,7-dioxo-N1-1-piperidinyl-, (6aS,10S,10aS,11aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



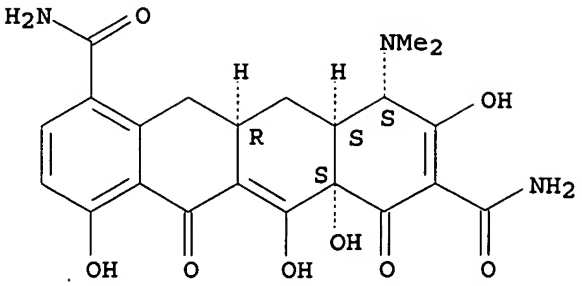
L8 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:371069 CAPLUS
DN 140:386006
TI Substituted tetracycline compounds for the treatment of malaria
IN Draper, Michael; Nelson, Mark L.
PA Paratek Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 161 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004038001	A2	20040506	WO 2003-US33927	20031024
	WO 2004038001	A3	20041111		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2502464	AA	20040506	CA 2003-2502464	20031024
	EP 1556007	A2	20050727	EP 2003-781398	20031024
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP 2006503898	T2	20060202	JP 2004-547165	20031024
PRAI	US 2002-421259P	P	20021024		
	WO 2003-US33927	W	20031024		

OS MARPAT 140:386006
AB The invention provides a method for treating or preventing malaria in a subject. The method includes administering to the subject an effective amount of a substituted tetracycline compound, such that malaria is treated or prevented. In one aspect, the invention relates to pharmaceutical compns. which include an effective amount of a tetracycline compound to treat malaria in a subject and a pharmaceutically acceptable carrier. The substituted tetracycline compds. of the invention can be used to in combination with one or more antimalarial compds. or can be used to treat or prevent malaria which is resistant to one or more other antimalarial compds. Compound preparation is described.
IT **685859-18-1**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetracycline derivs. for malaria treatment)
RN 685859-18-1 CAPLUS
CN 1,8-Naphthacenedicarboxamide, 10-(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-5,7-dioxo-, (6aS,10S,10aS,11aR)- (9CI)

(CA INDEX NAME)

Absolute stereochemistry.

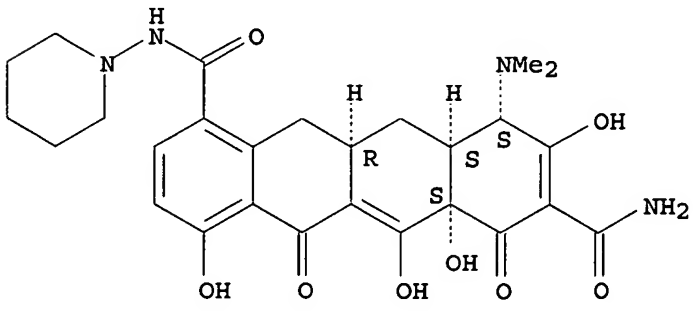


L8 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:371068 CAPLUS
DN 140:386057
TI Methods of using substituted tetracycline compounds to modulate RNA, and therapeutic use
IN Levy, Stuart B.; Draper, Michael; Jones, Graham; Nelson, Mark L.
PA Paratek Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004038000	A2	20040506	WO 2003-US33926	20031024
	WO 2004038000	A3	20041111		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2503446	AA	20040506	CA 2003-2503446	20031024
	US 2004214800	A1	20041028	US 2003-692764	20031024
	EP 1562608	A2	20050817	EP 2003-781397	20031024
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP 2006503897	T2	20060202	JP 2004-547164	20031024
PRAI	US 2002-421248P	P	20021024		
	WO 2003-US33926	W	20031024		

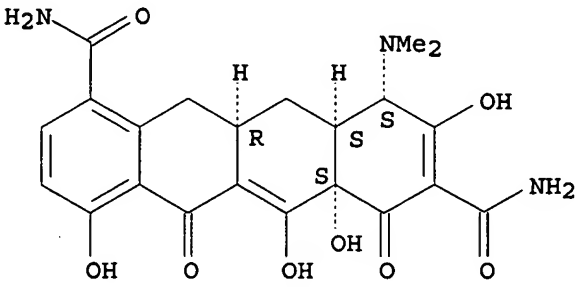
OS MARPAT 140:386057
AB A method for modulating RNA with tetracycline compds. is described. The invention also discloses a method for treating a subject for a disorder treatable by modulation of RNA or by modulation of RNA in combination with a second agent. Compound preparation is also described.
IT **488818-96-8 685859-18-1**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(RNA-modulating substituted tetracycline compds., and therapeutic use)
RN 488818-96-8 CAPLUS
CN 1,8-Naphthacenedicarboxamide, 10-(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-5,7-dioxo-N1-1-piperidinyl-, (6aS,10S,10aS,11aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 685859-18-1 CAPLUS
CN 1,8-Naphthacenedicarboxamide, 10-(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-5,7-dioxo-, (6aS,10S,10aS,11aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

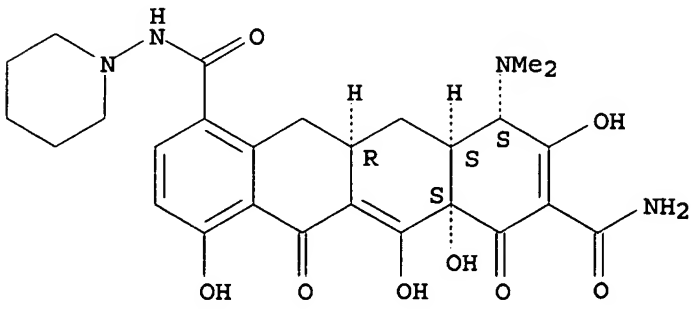


L8 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:57866 CAPLUS
DN 138:117673
TI Tetracycline compounds having target therapeutic activities
IN Levy, Stuart B.; Draper, Michael; Nelson, Mark L.; Jones, Graham
PA Paratek Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003005971	A2	20030123	WO 2002-US22451	20020715
	WO 2003005971	A3	20031127		
	WO 2003005971	C1	20040506		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004063674	A1	20040401	US 2002-196010	20020715
	EP 1408987	A2	20040421	EP 2002-748169	20020715
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
	JP 2004537544	T2	20041216	JP 2003-511780	20020715
PRAI	US 2001-305546P	P	20010713		
	US 2002-395741P	P	20020712		
	WO 2002-US22451	W	20020715		

OS MARPAT 138:117673
AB Methods and compds. for treating a variety of diseases with tetracycline compds. having a target therapeutic activity are described, as is compound preparation
IT **488818-96-8**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetracycline compds. with target therapeutic activities)
RN 488818-96-8 CAPLUS
CN 1,8-Naphthacenedicarboxamide, 10-(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-5,7-dioxo-N1-1-piperidinyl-, (6aS,10S,10aS,11aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

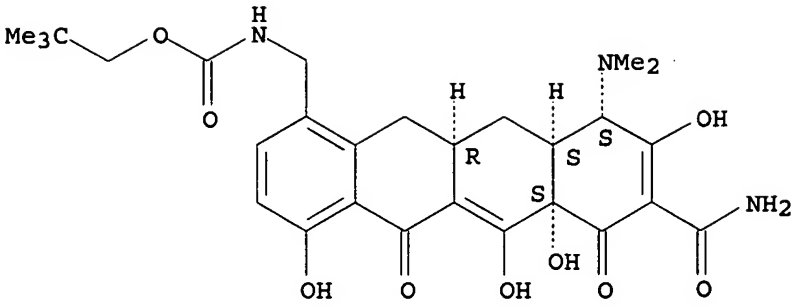


AN 2002:51420 CAPLUS
DN 136:102232
TI Preparation of 7-substituted tetracycline derivatives for pharmaceutical use as antibacterial agents
IN Nelson, Mark L.; Frechette, Roger; Viski, Peter; Ismail, Mohamed; Bowser, Todd; Bhatia, Beena; Messersmith, David; McIntyre, Laura; Koza, Darrell; Rennie, Glen; Sheahan, Paul; Hawkins, Paul; Verma, Atul; Warchol, Tad; Bandarage, Upul
PA Trustees of Tufts College, USA; Paratek Pharmaceuticals, Inc.
SO PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002004407	A2	20020117	WO 2001-US20766	20010629
	WO 2002004407	A3	20020404		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2415718	AA	20020117	CA 2001-2415718	20010629
	US 2003055025	A1	20030320	US 2001-895812	20010629
	US 6818635	B2	20041116		
	EP 1301466	A2	20030416	EP 2001-950674	20010629
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2001012265	A	20030624	BR 2001-12265	20010629
	JP 2004502753	T2	20040129	JP 2002-509075	20010629
	ZA 2003000750	A	20040211	ZA 2003-750	20030127
	US 2004224928	A1	20041111	US 2004-853635	20040524
PRAI	US 2000-216760P	P	20000707		
	US 2001-275576P	P	20010313		
	US 2001-895812	A1	20010629		
	WO 2001-US20766	W	20010629		

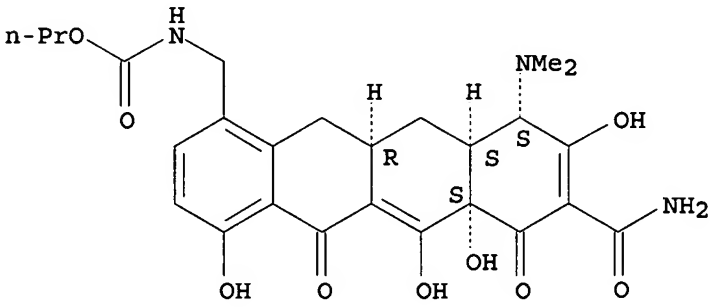
OS MARPAT 136:102232
IT **389625-03-0P 389625-13-2P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 7-substituted tetracycline derivs. for pharmaceutical use as antibacterial agents)
RN 389625-03-0 CAPLUS
CN Carbamic acid, [[(6aS,10S,10aS,11aR)-8-(aminocarbonyl)-10-(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-5,7-dioxo-1-naphthacenyl]methyl]-, 2,2-dimethylpropyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 389625-13-2 CAPLUS
CN Carbamic acid, [[(6aS,10S,10aS,11aR)-8-(aminocarbonyl)-10-(dimethylamino)-5,6a,7,10,10a,11,11a,12-octahydro-4,6,6a,9-tetrahydroxy-5,7-dioxo-1-naphthacenyl]methyl]-, propyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AN 1974:477746 CAPLUS
DN 81:77746
TI Tetracycline derivatives
IN Bernardi, Luigi; Colonna, Vincenzo; De Castiglione, Roberto; Masi, Paolo
PA Societa Farmaceutici Italia
SO Ger. Offen., 39 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 2346535	A1	19740411	DE 1973-2346535	19730915
	DE 2346535	B2	19800911		
	DE 2346535	C3	19810521		
	NL 7312648	A	19740320	NL 1973-12648	19730913
	NL 158172	B	19781016		
	CA 999855	A1	19761116	CA 1973-181034	19730913
	FR 2208885	A1	19740628	FR 1973-33067	19730914
	JP 49069653	A2	19740705	JP 1973-104458	19730914
	JP 57041458	B4	19820903		
	ZA 7307317	A	19740925	ZA 1973-7317	19730914
	AU 7360333	A1	19750320	AU 1973-60333	19730914
	BE 804913	A1	19740318	BE 1973-135695	19730917
	AT 7307996	A	19750615	AT 1973-7996	19730917
	AT 328613	B	19760325		
	US 3901942	A	19750826	US 1973-397691	19730917
	GB 1413347	A	19751112	GB 1973-43564	19730917
	HU 167850	P	19751225	HU 1973-SO1098	19730917
	ES 418809	A1	19760316	ES 1973-418809	19730917
	SU 574145	D	19770925	SU 1973-1957942	19730917
PRAI	IT 1972-29328	A	19720918		

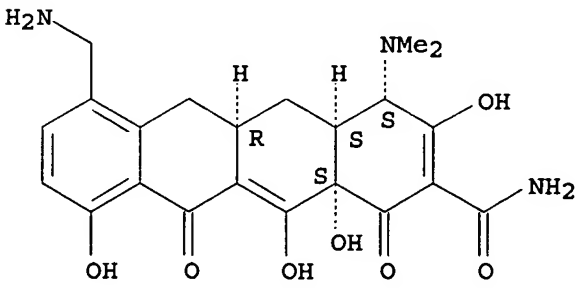
GI For diagram(s), see printed CA Issue.

AB Tetracycline derivs. I (R = H, R1 = e.g., Me, NH2, Me2NCH2, F3CCONHCH2; R2 = H, Me; R3 = H, OH) were prepared by the selective alkylation of a tetracycline derivative in the 9-position, followed by electrophilic substitution in the 7-position and dealkylation. Thus, I (R = R1 = R2 = R3 = H) was alkylated with Me2C:CH2 in (Me2N)3PO to give I (r = Me3C; R1 = R2 = R3 = H) which was nitrated with KNO3 and HF, then hydrogenated over PtO2 to give I (R = Me3C, R1 = NH2, R2 = R3 = H). Reaction of this product with HCHO in the presence of Pd-C followed by dealkylation with F3CSO3H in PhOMe gave I (R = R2 = R3 = H, R1 = Me2N). About 20 I were prepared

IT **53108-38-6P 53108-41-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

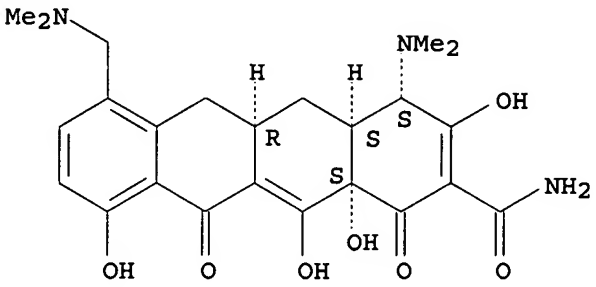
RN 53108-38-6 CAPLUS
CN 2-Naphthacenecarboxamide, 7-(aminomethyl)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, (4S,4aS,5aR,12aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 53108-41-1 CAPLUS
CN 2-Naphthacenecarboxamide, 4-(dimethylamino)-7-[(dimethylamino)methyl]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, [4S-(4α,4aα,5aα,12aα)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



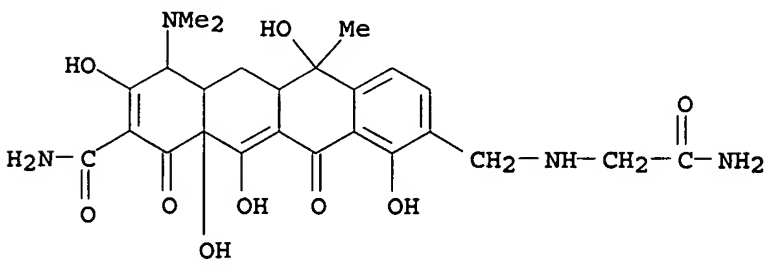
AN 1963:448189 CAPLUS
DN 59:48189
OREF 59:8679a-b
TI Tetracycline derivatives
PA Carlo Erba Societa per Azioni
SO 3 pp.
DT Patent
LA Unavailable

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI GB 921252		19630320	GB		<--
DE 1147576			DE		
PRAI IT		19600309			

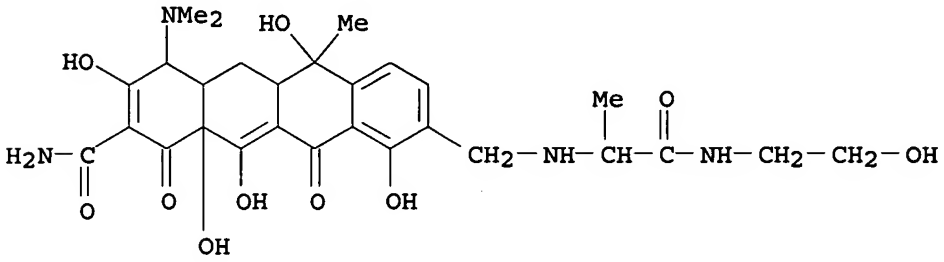
AB H2O-soluble tetracycline derivs. are prepared with HCHO and an α-amino acid amide. For example, 0.6 cc. 38% HCHO and 0.6 g. l-alaninamide are added to a solution containing 3 g. tetracycline in 120 ml. MeOH. After 2 hrs., the clear solution is evaporated and diluted with Et2O to precipitate the solid, which is filtered off and dried in vacuo at 50°, m. 150-6°, C26H32N4O9.

=> d hitstr 6

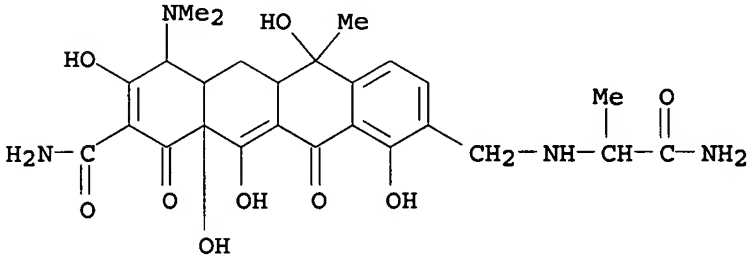
L5 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN
IT **96670-08-5**, 2-Naphthacenecarboxamide, 9-[[(carbamoylmethyl)amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- **96867-69-5**, 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-9-[[[1-[(2-hydroxyethyl)carbamoyl]ethyl]amino]methyl]-6-methyl-1,11-dioxo- **96967-72-5**, 2-Naphthacenecarboxamide, 9-[[(1-carbamoylethyl)amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- **96967-73-6**, 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-9-[[[(methylcarbamoyl)methyl]amino]methyl]-1,11-dioxo- **97828-43-8**, 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-9-[[[[(2-hydroxyethyl)carbamoyl]methyl]amino]methyl]-6-methyl-1,11-dioxo- **97879-49-7**, 2-Naphthacenecarboxamide, 9-[[[5-amino-1-[(2-hydroxyethyl)carbamoyl]pentyl]amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- **97924-11-3**, 2-Naphthacenecarboxamide, 9-[[(5-amino-1-carbamoylpentyl)amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-
(preparation of)
RN 96670-08-5 CAPLUS
CN 2-Naphthacenecarboxamide, 9-[[(carbamoylmethyl)amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- (7CI) (CA INDEX NAME)



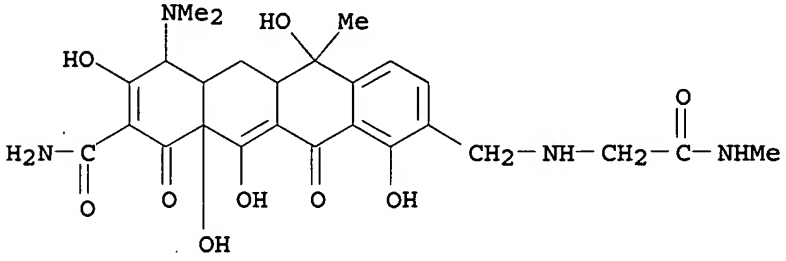
RN 96867-69-5 CAPLUS
CN 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-9-[[[1-[(2-hydroxyethyl)carbamoyl]ethyl]amino]methyl]-6-methyl-1,11-dioxo- (7CI) (CA INDEX NAME)



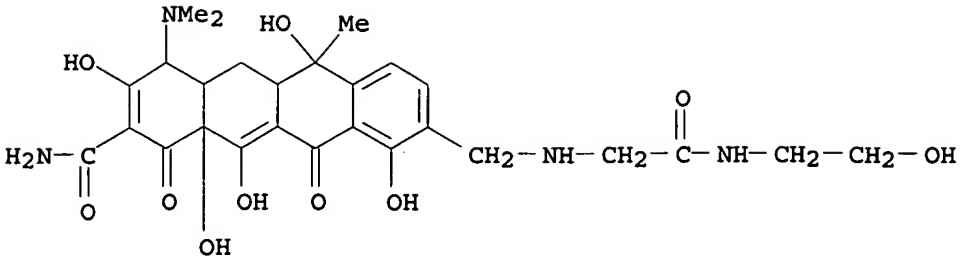
RN 96967-72-5 CAPLUS
CN 2-Naphthacenecarboxamide, 9-[[(1-carbamoylethyl)amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- (7CI) (CA INDEX NAME)



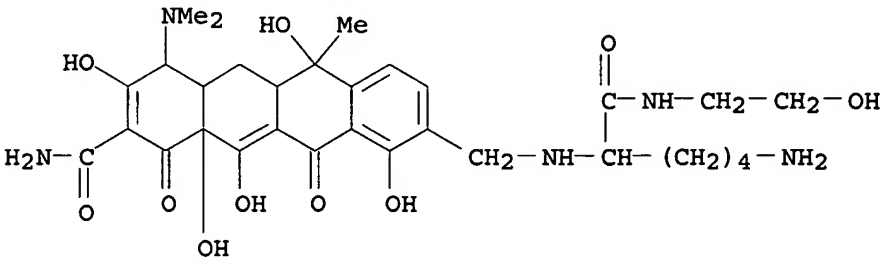
RN 96967-73-6 CAPLUS
CN 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-9-[[[(methylcarbamoyl)methyl]amino]methyl]-1,11-dioxo- (7CI) (CA INDEX NAME)



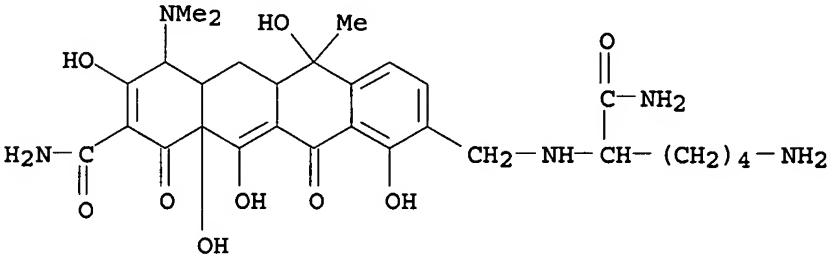
RN 97828-43-8 CAPLUS
CN 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-9-[[[[(2-hydroxyethyl)carbamoyl]methyl]amino]methyl]-6-methyl-1,11-dioxo- (7CI) (CA INDEX NAME)



RN 97879-49-7 CAPLUS
CN 2-Naphthacenecarboxamide, 9-[[[5-amino-1-[(2-hydroxyethyl)carbamoyl]pentyl]amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- (7CI) (CA INDEX NAME)



RN 97924-11-3 CAPLUS
CN 2-Naphthacenecarboxamide, 9-[[(5-amino-1-carbamoylpentyl)amino]methyl]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo- (7CI) (CA INDEX NAME)



PATENT SPECIFICATION

921,252

Date of Application and filing Complete Specification: March 9, 1961. *No. 8743/61*

Application made in Italy (No. 4065) on March 9, 1960

Complete Specification Published: March 20, 1963

Index at Acceptance:—Class 2(3), AA(1C2C:2A4).

International Classification:—C07d.

COMPLETE SPECIFICATION

NO DRAWINGS

New Tetracycline Derivatives

We, CARLO ERBA S.p.A., an Italian Body Corporate, of Via Imbonati 24, Milan, Italy, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to tetracycline derivatives.

It is known that tetracycline salts are not stable in aqueous solutions having a nearly neutral pH. They tend to form precipitates and their pharmacological application is therefore difficult.

The present invention provides soluble tetracycline derivatives which avoid this inconvenience and have a practically neutral reaction.

The tetracycline derivatives of the present invention are made by condensing together tetracycline, oxytetracycline, chlortetracycline, demethyltetracycline, or demethylchlortetracycline, with formaldehyde and an amide of an α-amino acid having the following structure:

$$R—CH(NH_2)—CONR^1R^2$$

where R is hydrogen, alkyl or substituted alkyl such that the compound $RCH(NH_2)COOH$ is a known, naturally-occurring amino-acid and R^1 and R^2 may be the same or different and represent hydrogen, alkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl or R^1 is hydrogen and R^2 is amino. Preferably R is such that the amino acid

$$R—CH(NH_2)—COOH$$

is glycine, alanine, serine or lysine. The preferred amides are the unsubstituted amides and the *N*-(β-hydroxyethyl)- and *N,N*-di(β-hydroxyethyl)-amides. The lower alkyl substituted amides, such as the mono- or dimethyl or ethyl amides are also useful. The term "lower alkyl" is used herein to refer to alkyl of up to six carbon atoms.

The tetracycline derivatives of the invention are Mannich-type condensation products having the formula:

$$T—CH_2—NH—CH(R)—CO—NR^1R^2$$

where T is a radical derived from tetracycline, oxytetracycline, chlortetracycline, demethyltetracycline, or demethylchlortetracycline by removal of a hydrogen atom, believed to be that *ortho* to the phenolic hydroxyl group, and R, R^1 and R^2 are as defined above, and obtainable by the condensation of a said tetracycline with formaldehyde and an α-aminoacid amide by the process defined above. In any case the analysis of the compounds of the invention indicates that their molecules consist of a radical derived from the tetracycline and a radical derived from the amide joined by a methylene group (derived from the formaldehyde).

The condensation of the tetracycline, formaldehyde and α-amino acid amide is conveniently carried out in an inert solvent, e.g. methanol, dioxane, or dimethylformamide, at room or slightly elevated temperature. The formaldehyde used can be gaseous, in aqueous solution (e.g. formalin), or in the form of the trimer (trioxane).

The following Examples illustrate the invention.

EXAMPLE I

0.6 cc. Formaldehyde (38% aqueous solution) and 0.6 g. l-alaninamide are added to a solution of 3 g. of tetracycline free base in 120 cc. methanol. A clear solution is obtained and allowed to stand for 2 hours. It is then evaporated to a small volume and diluted with diethyl ether. A precipitate forms and is filtered off and dried *in vacuo* at 50°C. The product thus obtained is a yellow powder melting at 150-156°C.

[Price 4s. 6d.]

Analysis:
Calc. for $C_{25}H_{32}N_4O_9$:
C 57.34% H 5.92% N 10.29% O 26.44%.
Found:
C 56.85% H 5.71% N 10.25% O 26.84%.

Similar soluble compounds can be obtained by following the procedure of this Example but employing; in place of tetracycline itself, chlortetracycline, oxytetracycline, demethyltetracycline, or demethylchlortetracycline; and, in place of alaninamide, glycinamide hydrochloride, l-lysinamide, serinamide, monomethylamide glycine, or diethylamide glycine.

The product obtained by reacting tetracycline with formaldehyde and glycinamide hydrochloride has a melting point of 148-152°C. The corresponding compounds when l-lysinamide, serinamide, and the monomethylamide of glycine are used have melting points of 145-150°C., 160-163°C., and 134-138°C. respectively.

EXAMPLE II

0.6 cc. Formaldehyde solution and 1.8 g. of the β-hydroxyethylamide of d,l-α-alanine are added to a solution of 6 g. of tetracycline in 200 cc. dimethylformamide. The solution is kept at 40°C. for 2 hours, and then concentrated to a small volume under vacuum and diluted with diethyl ether. The precipitate which forms is filtered off and dried *in vacuo* at 50°C. The product thus obtained is a yellow powder melting at 130-140°C.

Analysis:
Calc. for $C_{28}H_{35}N_5O_{10}$:
C 57.13% H 6.16% N 9.51% O 27.18%.
Found:
C 55.15% H 6.12% N 8.88% O 27.49%.

Similar products can be obtained using β-hydroxyethylamide-glycine, when the product has m.p. 135-138°C., β-hydroxyethylamide l-lysine, when the product has m.p. 130-135°C., or β-hydroxyethylamide d-serine in place of the β-hydroxyethylamide of d,l-α-alanine.

EXAMPLE III

1.1 cc. Formaldehyde (38% aqueous solution) and 1.8 g. of the diethanolamide of glycine are added to a solution of 5 g. tetracycline in 150 cc. dioxane. The solution is kept at room temperature for 2 hours and is then evaporated to a small volume. Tetracyclinemethylenediethanolamide glycine precipitates on adding diethyl ether.

Similarly can be obtained: tetracycline-methylene-diethanolamide d,l-alanine; tetracycline-methylene-diethanolamide l-lysine; and tetracycline-methylene-diethanolamide serine.

The invention provides also pharmaceutical compositions comprising one or more of the new tetracycline derivatives in association with a pharmaceutical carrier. Such compositions are preferably made up in a form suitable for oral or parenteral administration.

For oral administration the new compounds can be mixed with conventional diluents and tabletting materials and made up into tablets, pills and powders (which may be encapsulated). Alternatively the new compounds can be incorporated in a conventional syrup base.

For parenteral administration (for which they are especially suited), the new compounds may be dissolved in water, or another known injectable medium such as physiological saline, and the compositions sterilized, and filled into ampoules for storage before use.

WHAT WE CLAIM IS:—

1. Process for the preparation of water-soluble derivatives of a tetracycline which comprises reacting tetracycline, oxytetracycline, chlortetracycline, demethyltetracycline, or demethylchlortetracycline, with formaldehyde, and an α-amino-acid amide of the formula:

$$R—CH(NH_2)—CO—NR^1R^2$$

where R is hydrogen, alkyl or substituted alkyl such that the compound $RCH(NH_2)COOH$ is a known, naturally occuring amino acid and R^1 and R^2 may be the same or different and represent hydrogen, alkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, or dialkylaminoalkyl or R^1 is hydrogen and R^2 is amino.

2. Process according to claim 1 in which R is such that the amino-acid

$$RCH(NH_2)COOH$$

is glycine, alanine, serine or lysine.

3. Process according to claim 1 in which tetracycline, oxytetracycline, chlortetracycline, demethyltetracycline, or demethylchlortetracycline is reacted with formaldehyde and either the amide, or the *N*-β-hydroxyethylamide, or the *N,N*-di(β-hydroxyethyl)amide of glycine, alanine, serine, or lysine.

4. Process according to any of claims 1 to 3 in which the reaction is carried out in an inert solvent.

5. Process according to claim 1 substantially as described in any of Examples I to III.

6. Water-soluble tetracycline derivatives of the formula:

$$T—CH_2—NH—CH(R)—CO—NR^1R^2$$

where T is a radical derived from tetracycline, oxytetracycline, chlortetracycline, demethyltetracycline, or demethylchlortetracycline by removal of a hydrogen atom and R, R^1 and R^2 are as defined in claim 1, and obtainable by the condensation of a said tetracycline with formaldehyde and an α-amino acid amide in accordance with the process of any one of claims 1-5.

7. Tetracycline derivatives as claimed in claim 6 in which the residue R is such that

the acid

$$R—CH(NH_2)—COOH$$

is alanine, glycine, lysine or serine.

8. Tetracycline derivatives as claimed in claim 6 or 7 in which R^1 and R^2 are each hydrogen or β-hydroxyethyl.

9. A water-soluble tetracycline derivative as claimed in claim 6 substantially as described in any of the foregoing Examples.

10. A water-soluble tetracycline derivative obtained by the process of any one of claims 1 to 5.

11. A pharmaceutical composition comprising one or more of the compounds claimed in any of claims 6-10 in association with a pharmaceutical carrier.

J. A. KEMP & CO.,
Chartered Patent Agents,
14 South Square, Gray's Inn,
London, W.C.1.

Berwick-upon-Tweed: Printed for Her Majesty's Stationery Office by The Tweeddale Press Ltd.—1963
Published at The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.